heading before the second paragraph. Such an amendment should not constitute new matter given that the exact same amendment was entered without objection in applicant's parent application, 07/984,264, now U.S. Patent 5,432,099 which was also examined by Dr. Woodward. Accordingly, this same specification amendment is included in the present submission.

Also in accordance with the present submission, claim 1 has been amended to recite that "each spot has a high coating density of one of said binding agents". This recitation together with the recitation that "not more than 0.1 V/K moles of binding agent are present on any spot" is believed to clearly distinguish claim 1 over the combined disclosures of WO 84/01031 and Chen et al. The same is true with respect to claim 4 and newly presented claim 9, which also include these same recitations.

New claims 9-12 which are presented herewith are directed to a four-step method for determining a plurality of analytes in a liquid sample. This embodiment of applicant's invention is described in present specification at pages 6, 7, 13 and 14.

No new matter is being introduced into this application by reason of any of the foregoing amendments.

Although the Advisory Action does not so state, it is assumed that the rejection of claims 1-3 as allegedly anticipated by Ekins et al. (1989), the rejection of claims 1 and 2 as allegedly anticipated by WO 88/01058 and the rejection of claim 3 as allegedly obvious over WO 88/01058 in view of the commercial availability of the BioRad Laser Sharp MRC500 have all been withdrawn in view of the submission of applicant's Substitute Declaration in response to the September 2, 1997 Official Action. If applicant is mistaken in this assumption, it is respectfully requested that the Examiner indicate that such is the case in the next Official Action.

Thus, the only ground of rejection outstanding is the 35 U.S.C. §103 rejection of claims 1-8, based on the combined disclosures of WO 84/01031 and Chen et al. (U.S.

Patent 4,385,126). This remaining ground of rejection is respectfully traversed.

All of applicant's independent claims call for "loading a plurality of different binding agents . . . onto a support means at a plurality of spaced apart small spots such that each spot has a high coating density of one of said binding agents but not more than 0.1 V/K moles of binding agent are present on any spot . . ." The disclosure of WO 84/01031 does not teach or suggest these conditions. The smallest amount of receptor used in the method described in WO 84/01031 is 0.25 V/K, which is well in excess of the amount recited in claims 1, 4 and 9 herein. There is nothing in the disclosure of WO 84/01031 to suggest that a smaller amount of receptor be used or that the method described therein could be "optimized" by using a smaller amount of receptor than that which was specifically exemplified. Consequently, the Examiner's position regarding the obviousness of these conditions is based essentially on the purported logical appeal of optimizing the method of Ekins WO 84/01031. The previously submitted Declaration of Johann Berger speaks to the non-obviousness of applicant's analyte determination method, stating that it provides sensitivity enhancement, with shorter incubation times, by immobilizing small amounts of binding agent at high density in microspots. The Examiner considers Dr. Berger's Declaration insufficient to overcome the §103 rejection, in effect, because it lacks "a logical basis". Logic, however, cannot supply the motivation necessary for establishing obviousness when it flies in the face of the accumulated knowledge and experience of those skilled in the art, as in the present case.

The assay determination method of this invention cannot reasonably be considered obvious absent some suggestion in WO 84/01031 to operate the assay described therein using small spots of binding agent having a high coating density with not more than 0.1 V/K moles present on any spot. Dr. Berger's Declaration addresses this point and concludes that

such a suggestion is not provided by WO 84/01031, because of an expected loss of sensitivity leading to an increase in incubation time. Dr. Berger's statement in this regard is made "notwithstanding the disclosure in Ekins '031". See paragraph 5 of Dr. Berger's Declaration. Thus, the Examiner's observation that "Berger speaks to what artisans were doing but not what they would have done following a reading of Ekins" (at page 2 of the Advisory Action) is simply inaccurate.

The Declarations of Stuart Woodhead and Roger P. Ekins submitted herewith also address, in part, the question of what those of ordinary skill in the art would have derived from the disclosure of WO 84/01031, as of 1987, with regard to the amount of binding agent to be used therein. Dr. Woodhead states:

> [W]hen I heard Ekins describe his method for the measurement of ambient analyte concentrations, it seemed to me that while the concept was attractive, the requirement to reduce the amount of binding reagent in such assays would inherently restrict their application to situations where high sensitivity was not required. I would thus contend that it would be far from obvious that the use of immobilized microspots of small amounts of antibody could actually provide a basis for highly sensitive immunoassays. To my mind, such a possibility is not disclosed by Ekins '031 [paragraph 4 of Dr. Woodhead's Declaration].

Dr. Woodhead's Declaration goes on to state:

> The equation and teaching in Ekins '031 relate to the construction of assays which are sample-volume independent. While this is in itself a desirable goal, the equations in Ekins '031 are not concerned with the issue of assay sensitivity and so they do not suggest that, under certain circumstances, using a small amount of binding agent could enhance sensitivity.

> Thus, in my opinion, the disclosure in Ekins '031 does not teach or suggest the claimed invention to a person of ordinary skill in the art [paragraph 5 of Dr. Woodhead's Declaration].

Furthermore, regarding the Examiner's citation of the Chen et al. patent, Dr. Woodhead states:

> Chen et al. fails to disclose or suggest that the use of such a small amount of binding agent in an assay with a reaction time as short as assays of conventional design that employ large amounts of antibody could provide comparable or even better sensitivity [paragraph 6 of Dr. Woodhead's Declaration].

Furthermore, regarding the alleged obviousness of "optimizing the method of WO 84/01031", Professor Ekins' Declaration states:

> [I]t is important to realize that Ekins '031 and in particular the equations set out in this application do not relate to assay sensitivity nor do they in any way suggest that use of a small amount of binding agent could - under certain circumstances - enhance sensitivity [paragraph 3 of Professor Ekins' Declaration].
>
> . . .
>
> [A] person of ordinary skill in the art would inevitably conclude that an assay designed in accordance with Ekins '031 to be independent of sample volume would concomitantly suffer a considerable loss in sensitivity. Nothing in the equations in this application would lead the person of ordinary skill in the art to think otherwise, nor point to the way in which the loss of sensitivity thought to be an inevitable consequence of the use of a small amount of binding agent might be overcome [paragraph 5 of Professor Ekins' Declaration].

. . .

> Ekins '031 in no way indicates that contemporary teachings in 1987 and relating to the design of high sensitivity assays were wrong. Thus, there is no reason based on Ekins '031 to suppose that those of ordinary skill in the art would re-examine the results of their past optimization experiments or that any further experiments of this nature would reverse conclusions widely accepted in the art regarding the disadvantages of the use of low binding agent concentrations in regard to sensitivity [paragraph 9 of Professor Ekins' Declaration].

In summary, there is no factual basis in the record to support the Examiner's contention that it would have been obvious to practice the method of WO 84/01031 using small spots of binding agent having a high coating density, with not more than 0.1 V/K moles present on any spot. Indeed, the evidence of record is overwhelmingly to the contrary.

Turning to the dual labelling aspect of applicant's method, which is a commercially important and patentably significant feature of this invention, Dr. Berger's Declaration is to the effect that immobilization of a known amount of binding agent to a test support during manufacture is inconsequential in practicing the method of this invention, as it is independent of the amount of binding agent used. The Examiner dismisses Dr. Berger's view in this regard as "illogical and contradictory". To the contrary, the averments in paragraph 7 of Dr. Berger's Declaration are part and parcel of the inventiveness of applicant's claimed method.

If one were to employ dual labelling in the method of WO 84/01031 for the reasons specified in the Chen et al. patent, i.e., to ensure immobilization of a constant amount of binding agent to a test support for quality control and/or to compensate for instrumental errors, he/she would be missing a distinct operating advantage of the present invention. This

advantage lies in the fact that applicant's method is independent of the amount of receptor used. In other words, it does not matter that the amount of receptor immobilized on the test support varies when practicing this invention. The importance of this advantage cannot be emphasized enough. Commercial manufacturers have expended and continue to expend substantial time, effort and money in developing materials and methods suitable for accurately depositing receptor on test supports. The method of the present invention bypasses these problems since it is not necessary to know the amount of the receptor immobilized on the test support, or even that it be known to be constant. An advantage such as this should be considered in determining patentability, irrespective of whether or not it is expressly recited in the claims. *In re Estes*, 164 USPQ 519 (CCPA 1970). The Examiner has apparently overlooked this advantage in assessing patentability in the present case.

As stated in the Declaration of Professor Ekins submitted herewith:

> In fact, the use of dual labelling in accordance with the instant specification relieves the assay manufacturer of having to know or to keep constant the exact amount of binding agent affixed to a support. That is in practicing the assay of the instant specification one simply needs to know that the total amount of binding agent present is less than the threshold level of 0.1 V/K moles. . . .
>
> This is quite contrary to the teaching in Chen et al. '126, where the use of a label attached to the 'capture' binding agent . . . . is explicitly intended to confirm that the standard amount of capture binding agent is present. . . In an assay performed in accordance with the instant specification it is unnecessary to determine how much binding agent is present, and it is therefore unnecessary (inter alia) to scan the entire area on which the binding agent is deposited. . .

> Moreover, manufacturers frequently encounter difficulties in ensuring that the same amount of binding agent is present in every incubation tube. Thus, it is distinct advantage of the present invention that one does not need to know the precise amount of binding agent present.

In view of the foregoing remarks, it should be apparent that the proposed combination of WO 84/01031 in view of the Chen et al. patent does not teach or suggest an assay which is independent of the amount of receptor, as neither of these references individually discloses a way of achieving this clearly desirable goal. References which do not recognize an applicant's problem cannot have suggested its solution. *In re Schaffer*, 108 USPQ 326 (CCPA 1956). Given that the combined disclosures of WO 84/01031 and the Chen et al. patent do not teach or suggest a way of solving the problem of making an assay independent of the amount of receptor used, this feature alone distinguishes the present invention from the prior art in a way which is both novel and nonobvious.

The rejection of claims 1-8 based on WO 84/01031, the Chen et al. patent and the commercial availability of the BioRad Laser Sharp MRC500 is untenable for at least the same reasons advanced above with regard to the impropriety of combining the disclosures of WO 84/01031 and the Chen et al. patent in the manner proposed by the Examiner.

It is once again requested that the requirement for corrected drawings be held in abeyance pending the indication of allowable subject matter.

In view of the present amendments, the Declaration of Dr. Berger already of record, the Declarations of Dr. Woodhead and Professor Ekins submitted herewith and the foregoing remarks, it is respectfully requested that the rejections set forth in the final Action of September 2, 1997 be withdrawn and that this application be passed to issue and

such action is earnestly solicited.

Respectfully submitted,

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Enclosures: Declaration of Roger Philip Ekins
Declaration of Stuart Woodhead